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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Application Number: 10/003,021
Filing Date: November 14, 2001
Appellant(s): FERNANDEZ ET AL.

Natalie A. Davis
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 05/31/2007 appealing from the Office action
mailed 02/01/2007.

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(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Dubensky, Jr. et al. US Patent 6,342,372. Issued 01/29/2002.

Guan et al. EP0286239. Published 10/12/1988.

Gregoire et al. J Biol Chem. 1996 Dec 20;271(51): 32951-9.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 41-43 and 45-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dubensky, Jr. et al. (US Patent 6,342,372) in view Guan et al. (EP0286239) and Gregoire et al. (J Biol Chem. 1996 Dec 20;271(51):32951-9.) This rejection is set forth in the prior Office Action, mailed on 10/19/2005.

(10) Response to Argument

On pages 3-4 of the Appeal Brief, Appellants cite case law for establishing a *prima facie* case of obviousness. Appellants allege that the PTO must show suggestions that would compel one of ordinary skill to combine the cited references in order to make and use the claimed invention. Appellants allege that the PTO must consider prior art in their entirety including portions that teach away from the claimed invention. Appellants generally summarize some of the teachings of the references of Dubensky, Jr. et al., Guan et al, and Gregoire et al. on pages 4-6. On pages 6-7, Appellants generally summarizes the Examiner's position and Appellants position regarding claims 41-43 and 45-58.

Beginning on page 8, line1, of the Appeal Brief Appellants argue that the Examiner appears to be relying on hindsight in combining the references of Dubensky, Jr. et al., Guan et al., and Gregoire et al. in making the obviousness rejection, and that the Examiner has failed to consider parts of the references that teach away from the claimed invention.

Appellants argue on page 8, lines 4-11, that the Examiner has ignored that Dubensky's vectors are configured in a "bicistronic heterologous configuration" designed to prevent expression of fusion proteins.

Appellants argue on page 8, lines 12-18, that the Examiner's selective reading of Dubensky, and that the focusing on claim elements that are disclosed and combining those remaining elements in other references is an example of impermissible hindsight analysis.

Appellants allege on page 8, line 19 to page 9, line 3, that the Examiner has not provided any suggestions that would compel one of ordinary skill to combine the references to make and use the invention as claimed.

Appellants' arguments have been fully considered but are not found to be persuasive.

In response to Appellants' argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the Appellants' disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

The Dubensky Jr. et al. reference teaches eukaryotic vectors for the production of recombinant proteins in which the vectors include an oligonucleotide primer comprising the CACC sequence (SEQ ID No. 69) linked to the 5' start codon ATG of nucleic acids encoding heterologous polypeptides, where the sequences surrounding the ATG start codon from base -9 to +1 that conform to the Kozak consensus sequence for efficient translational initiation (see entire publication, especially column 90, lines 46-58). Dubensky, Jr. et al. teach that the eukaryotic expression vectors containing the above described nucleic acids have promoters, enhances, selection marker sequence, and origin of replication (see entire patent, especially Figures 8, 11, and 15; and column 2, line 63 to column 50, line 55).

The rationale for using the Dubensky Jr. et al. reference as the primary reference is that the taught CACC sequence (SEQ ID No. 69) linked to the 5' start codon ATG of nucleic acids encoding heterologous polypeptides and the sequences surrounding the ATG start codon from base -9 to +1 conform to the Kozak consensus sequence for efficient translational initiation, which is advantageous and beneficial for heterologous protein expression. Although the Dubensky Jr. et al. reference teaches vectors configured in a "bicistronic heterologous configuration", where heterologous genes in the bicistronic vectors are separated by a stop codon so that the encoded proteins are expressed separately, one of ordinary skill in the art, in view of the well developed art of recombinant molecular biology and heterologous protein expression, would modify the expression vector of Dubensky, Jr. et al. such that stop codons are not introduced which

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may prevent protein expression. This was stated in the Advisory Action dated 01/29/2007 and is further explained below.

At the time the claimed invention was made, recombinant molecular biology and heterologous protein expression methods and techniques were well established and known to those of ordinary skill in the art. Appellants' own specification cites the recombinant molecular biology textbook "Molecular Cloning: A Laboratory Manual", second edition, edited by Sambrook, Fritsch, & Maniatis (Cold Spring Harbor Laboratory, (1989)), which teaches and describes modification and manipulation of vectors including plasmid vectors. According to MPEP 2143.02, the prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Thus, it is within the capabilities of one of ordinary skill in the art to successfully manipulate and modify the vectors of Dubensky Jr. et al. such that stop codons are removed or not introduced in the vectors which may prevent protein expression.

Appellants have not provided evidence that one of ordinary skill in the art cannot succeed in modifying and manipulating plasmid vectors to remove stop codons that may prevent protein expression. Appellants' arguments are tangential and do not directly address the obviousness rejection. Appellants have not addressed the main teaching of the Dubensky Jr. et al. reference, where the taught CACC sequence (SEQ ID No. 69) linked to the 5' start codon ATG of nucleic acids encoding heterologous polypeptides and the sequences surrounding the ATG start codon from base -9 to +1 conform to the

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Kozak consensus sequence for efficient translational initiation, which is advantageous and beneficial for heterologous protein expression. The obviousness rejection does not solely rest on the teachings of Dubensky, Jr. et al., but a combination of Dubensky, Jr. et al., Guan et al, and Gregoire et al., where the combination of references do not teach away from the claimed invention. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to Appellants' argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). The obviousness rejection is based on the combination of the references of Dubensky, Jr. et al., Guan et al, and Gregoire et al.

The reference of Dubensky, Jr. et al. is relied upon for providing a teaching, suggestion, or motivation to produce the claimed invention, where the taught CACC sequence (SEQ ID No. 69) linked to the 5' start codon ATG of nucleic acids encoding heterologous polypeptides and the sequences surrounding the ATG start codon from

base -9 to +1 conform to the Kozak consensus sequence for efficient translational initiation, which is advantageous and beneficial for heterologous protein expression.

Thus, inserting any DNA sequence encoding any protein 3' into the taught sequence of Dubensky, Jr. et al. would result in efficient translational initiation and subsequent expression and production the protein.

Although the Dubensky, Jr. et al. reference does not teach that the expression vectors are linked to an affinity purification tag or epitope tag, the secondary references of Guan et al. and Gregoire et al. were used in combination with the teachings of Dubensky, Jr. et al. to meet the claim limitations.

The secondary reference of Guan et al. teaches expression vectors, prokaryotic and eukaryotic host cells, and methods for making, expressing, isolating, and purifying any protein fused to the *E. coli* maltose binding protein (MBP); that these methods and products are useful for purifying virtually any hybrid polypeptide molecule employing recombinant techniques; and that DNA fragments coding for the target protein and MBP are linked with DNA segment coding for a peptide which is recognized and cut by a proteolytic enzyme for purposes of purifying the protein itself.

The secondary reference of Gregoire et al. teaches a recombinant form of horse allergen Equ c1 protein linked to a polyhistidine tag which was purified by immobilized metal affinity chromatography.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the vector of Dubensky, Jr. et al. such that the DNA encoding the MBP and DNA encoding a polypeptide that is recognized and cut by

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proteolytic enzymes as taught by Guan et al. is linked 3' to the CACC sequence (SEQ ID No. 69) that is linked to the 5' start codon ATG of nucleic acids encoding heterologous polypeptides as taught by Dubensky, Jr. et al. Furthermore, the teachings of Dubensky, Jr. et al. are modified to incorporate a polyhistidine tail as taught by Gregoire et al. for the purposes of purification by immobilized metal affinity chromatography. The modified vector of Dubensky, Jr. et al. would have the 5'-CACC sequence linked immediately to a start codon of an open reading frame (ORF), wherein the ORF is linked to a nucleic acid sequence encoding a heterologous polypeptide, and an affinity purification tag. Thus, the combination of the references of Dubensky, Jr. et al., Guan et al., and Gregoire et al. teaches or suggests the claim limitations.

According to MPEP 2144, the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Semaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). One of ordinary skill in the art at the time the invention was made would be motivated to modify the teachings of Dubensky, Jr. et al. as described above in order to express and purify heterologous polypeptides fused to MBP and a polypeptide that is recognized and cut by proteolytic enzymes, where the taught CACC sequence (SEQ ID No. 69) linked to the 5' start codon ATG of nucleic acids encoding heterologous polypeptides and the sequences surrounding the ATG start codon from base -9 to +1 conform to the Kozak

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consensus sequence for efficient translational initiation, which is advantageous and beneficial for heterologous protein expression.

Furthermore, Appellants have not provided evidence showing that there was no reasonable expectation of success. At the time the claimed invention was made, recombinant molecular biology and heterologous protein expression methods and techniques were well established and known to those of ordinary skill in the art. Appellants' own specification cites the recombinant molecular biology textbook "Molecular Cloning: A Laboratory Manual", second edition, edited by Sambrook, Fritsch, & Maniatis (Cold Spring Harbor Laboratory, (1989)), which teaches and describes modification and manipulation of vectors including plasmid vectors. Thus, combining the teachings of Dubensky, Jr. et al., Guan et al, and Gregoire et al. is within the capabilities of ordinary skill in the art, and would predictably yield a functioning plasmid vector that has the 5'-CACC sequence linked immediately to a start codon of an ORF, wherein the ORF is linked to a nucleic acid sequence encoding a heterologous polypeptide and an affinity purification tag.

The Examiner has determined the scope and contents of the prior art, ascertained the differences between the prior art and the claims at issue, and found the claimed invention to have been obvious in view of the combined teachings of the references.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

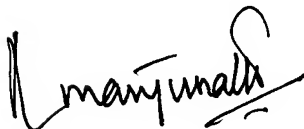
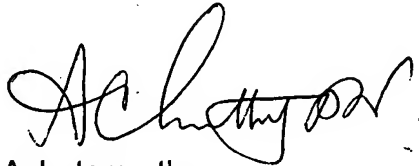
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For the above reasons, it is believed that the obviousness rejection should be sustained.

Respectfully submitted,
Christian L. Fronda
Patent Examiner
1652



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